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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,550	02/09/2001	Akihiro Funakoshi	053466/0299	5276
22428	7590	12/15/2008	EXAMINER	
FOLEY AND LARDNER LLP			SPECTOR, LORRAINE	
SUITE 500			ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 09/762,550	Applicant(s) FUNAKOSHI ET AL.
	Examiner Lorraine Spector	Art Unit 1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If no period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(o).

Status

- 1) Responsive to communication(s) filed on 09 October 2008.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 14, 16-23, 25 and 26 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 14, 16-23, 25, 26 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO/SB/08c)
 Paper No(s)/Mail Date _____
- 4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date _____
- 5) Notice of Informal Patent Application
 6) Other: _____

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/9/2008 has been entered.

Claims 14, 16-23, 25 and 26 are pending and under consideration. There have been no amendments to the claims since the response of 8/15/07.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

- (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 14, 16-23, 25 and 26 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sato et al., Cancer Research 53(4):851-6, February 1993, and/or Kishimoto et al., EP 0 791 359 A1, either or both references in view of Gross et al., Hepato-Gastroenterol.

40:522-530, cited by applicants, and Farkas et al., Neuroscience Letters 242(3):147-150. 2/20/98 for reasons of record in the previous Office Action mailed 10/6/2003.

Applicants arguments in the amendment filed 10/9/08 have been fully considered but are not deemed persuasive.

At page 2 of the response, applicants argue that if there were sufficient evidence of a causative link between IL-6 and acute pancreatitis, that such would have been made explicit in the art. This argument has been fully considered but is not deemed persuasive. It is not necessary that there have been an explicit teaching of such; the standard under 35 U.S.C. §103(a) is whether or not the person of ordinary skill in the art would have found the Invention *obvious* over the cited prior art. The examiner has established a *prima facie* case of obviousness; the cited art clearly indicates IL-6 to be a likely causative agent of acute pancreatitis. Further, even if it were merely associated with, and not a causative agent of acute pancreatitis, the person of ordinary skill in the art would have been motivated to administer an IL-6 antagonist in view of the fact that IL-6 is an inflammatory cytokine, acute pancreatitis is an inflammatory condition, and the art clearly indicates that IL-6 is elevated in acute pancreatitis. Therefore, applicants arguments as to whether IL-6 is merely causative or associated with the condition are moot.

As was stated in the previous Office Action, applicants argue that “That IL-6 was used as a biomarker for pancreatitis would not have motivated those of ordinary skill in the art to treat acute pancreatitis with IL-6 antagonists”, on the basis that a correlation is not tantamount to a causative effect. This argument has been fully considered but is not deemed persuasive because IL-6 was not merely a biomarker, but rather would have been expected by the person of ordinary skill in the art to have a causative effect in acute pancreatitis because of its well-known property of being an *inflammatory* cytokine (for Example, see Farkas’ abstract). Table 1 of Farkas clearly shows that serum IL-6 levels were greatly elevated at 4, 24 and 48 hours, compared to at 0 hours, becoming more elevated as the acute pancreatitis progressed. Gross specifically teaches that IL-6 is not only associated with, but predictive of the severity of acute pancreatitis. It simply begs credulity that these teachings would not suggest to the person of ordinary skill in the art that reduction of IL-6 levels in patients with acute pancreatitis would be beneficial. Clearly the secondary references teach that IL-6 is associated with acute pancreatitis. This, taken with the

teachings of the primary reference, to use anti-IL-6 antibodies to treat IL-6 associated conditions, clearly renders obvious the claimed invention. The examiner notes that this same argument was also found non-persuasive in the Office Actions mailed 2/3/2005 and 5/24/2004.

Applicants also argue that the Examiner is using "impermissible hindsight" in making the rejection. This argument has been fully considered but is not deemed persuasive. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In this case, no knowledge gleaned only from applicants disclosure was used in rejecting the claims.

In the underlined section of applicants arguments on page 4 of the response, applicants appear to be asserting unexpected results. This argument has been fully considered but is not deemed persuasive because the results obtained are exactly what the person of ordinary skill in the art would expect given the prior art. Applicants have provided no facts or evidence to the contrary.

At pages 4-5 of the response, applicants once again argue that the Knulst and Murata references teach against the success of the currently claimed invention. This argument has been once again fully considered but is not deemed persuasive. Once again, applicants allege that the reference "shows that in the GVHD mouse model, serum levels of IL-6 are increased, but that blocking the IL-6 using an IL-6 antibody was ineffective. This argument has been fully considered but is not deemed persuasive because Knulst et al. conclude in the abstract that "The results of this study suggest successive waves of cytokine-secreting cell populations consistent with the induction of an inflammatory response in the development of acute GVH disease", in other words that the IL-6 was secreted only over a specific period. This is a key key difference between GVHD and pancreatitis; applicants are citing references that are *further* from the claimed invention than those cited by the Examiner, which show a steady increase in the amount of IL-6. The references cited by the examiner relate not to GVHD, but to acute pancreatitis,

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which is the subject of the claims, and teach that there is an elevated and sustained IL-6 response in acute pancreatitis. The mice used in the GVHD study had been lethally irradiated, and then "reconstituted" with spleen cells only. The full range of immune cells was not present. Knulst et al. teach at page 35 that IL-6 levels increased at day 4, and were "significantly increased" from day 5 onward. On the contrary, anti-IL-6 antibodies were injected at day 1; see page 38; while the authors state that "detectable" levels of rat IgG occurred "for a period up to 14 days", it is not clear how much of the antibody was present when IL-6 production occurred and peaked. Further, in view of Farkas' table 1, it is entirely possible that the IL-6 levels merely exceeded the amount of antibody available to such an extent that the antibody was ineffective. Knulst's conclusion of "successive waves" of cytokine production are entirely consistent with Farkas' table 1. In summary, in view of the teachings of Gross and Farkas, which deal with the actual disease in question, the teachings of Knulst et al. are not sufficient to overcome the *prima facie* finding of obviousness.

At page 5, applicants argue the Murata reference. Applicants focus on TNF in acute pancreatitis, which is not at issue here. Of particular note, however, is the statement at page 3 of the translation of the document, which states that "acute phase reactants in the liver cell are induced mainly by IL-6." At page 4 of the translation, it is stated that "The IL-6 values at the early stage of severe acute pancreatitis were significantly higher than the other two groups, moderate and mild pancreatitis groups." They go on to state that they *assume* that the levels of IL-6 are due to TNF, but that such cannot (as of 1992) be measured accurately, and that they have to "conjecture that TNF and IL-1 levels were probably increased before the IL-6 elevation." At page 8 of the translation, it is stated that "the amount of TNF and IL-1 induced changes dependent on the degree of hte lesion and the amount of IL-1, IL-8 and CSF successively induced *should also be controlled*" (emphasis added). This would suggest inhibition of IL-6 as claimed by applicants. Therefore, applicants assertion that Murata would teach against inhibition of IL-6 is contrary to the teachings of Murata, and not persuasive.

Applicants suggestion at page 6 that administration of anti-TNF worsens acute pancreatitis has been fully considered but is not deemed persuasive because: (a) it has no bearing on the administration of anti-IL-6, which is the subject of the claims, (b) Murata is a theoretical paper, and does not administer anti-TNF nor any other treatment, and (c) it appears to be

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conjecture, and is not supported by any fact or evidence of record. Accordingly the argument is not persuasive.

With regard to the newly submitted abstract by Guice et al., they clearly indicate that the failure of administration of anti-TNF is likely to be due to the pleiotrophic nature of the effects of TNF, and would actually teach *toward* inhibiting the inflammatory cytokines directly, such as IL-6.

It is believed that all pertinent arguments are addressed.

Conclusion

No claim is allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

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If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Dr. Manjunath Rao, at telephone number 571-272-0939.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to **571-273-8300**. Faxed draft or informal communications with the examiner should be directed to **571-273-0893**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Lorraine Spector/
Primary Examiner, Art Unit 1647

Lorraine Spector, Ph.D.
Primary Examiner